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Restored Cognitive Function in Rats With Combined Denervations in the Temporal Region: Neurochemical Aspects

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MYHRER, T. *Restored cognitive function in rats with combined denervations in the temporal region: Neurochemical aspects.* PHARMACOL BIOCHEM BEHAV **62**(4) 683–688, 1999.—During early testing (1 week), there is a clear impairment of preference for novelty in rats with combined transections of the fiber connections between the temporal and lateral entorhinal cortices and the hippocampal perforant path (TC/LEC + PP lesions). During late testing (2–3 weeks), a complete recovery of the preference for novelty is seen. The purpose of this study was to pharmacologically examine whether cholinergic or glutamatergic systems might support the processes underlying the recovery. The cholinergic antagonist atropine sulfate caused a complete reappearance of the impaired preference for novelty in rats with TC/LEC + PP transections. The glutamatergic antagonist HA-966 only produced a moderate reactivation of the recovered lesion effect. A moderate impairment was also seen in intact rats treated with atropine or HA-966. The results suggest that blocking of cholinergic function impairs the recovered performance in this specific task without precluding the involvement of other uninvestigated neurochemical systems. © 1999 Elsevier Science Inc.

Temporal-hippocampal denervations Preference for novelty Recovery of function
Muscarinic receptors NMDA receptors

THE parahippocampal cortex (perirhinal and entorhinal cortices) seems to make up an important interface between the neocortical association areas and the hippocampal region (hippocampus proper, fascia dentata, and subiculum) in the rat, cat, and monkey (20). In the rat, information from all sensory modalities converges in the perirhinal cortex and is further transmitted to the hippocampal region by way of the entorhinal cortex (5). In return, the hippocampal region sends information to widespread cortical areas via the entorhinal cortex (8,22).

Exploration of a discrete novel object is one form of inquisitive activity frequently seen among rats. This activity appears as a strong preference for novelty, the recognition of which is probably based on polymodal sensory information (3). Transections of the fiber connections between the temporal cortex (TC) and the lateral entorhinal cortex (LEC) or transections of the hippocampal perforant path (PP) both result in reduced preference for novelty. Surprisingly, however, a combination of these types of lesions leads to a recovery of the preference for novelty during postoperative days 9–10 (16). A further analysis of this phenomenon has shown that during early testing (postoperative days 6–8) a clear deficit is seen in rats with TC/LEC + PP lesions, whereas normal preference for novelty occurs during late testing (postoperative days 15–17; Myhrer and Wangen, unpublished data). These unexpected findings may provide useful clues for investigations of mechanisms underlying spontaneous recovery of function.

Neurotransmission in TC and LEC is predominantly glutamatergic. Reduced high-affinity D-aspartate uptake in both TC and LEC is measured after TC/LEC transections (14), and systemic administration of glutamatergic agonists can completely restore memory function in rats with TC/LEC lesions (15). Also, the hippocampal afferents from the entorhinal cortices are believed to use glutamate as neurotransmitter (10). However, the second major hippocampal input, arising in the septal area, is believed to use acetylcholine as neurotransmitter (17,21).

In response to neural injury, both glutamatergic and cholinergic systems have been shown to react in a compensatory manner. Compensatory mechanisms have been seen to normalize glutamatergic axon terminal activity in the septum fol-

lowing loss of innervation from the frontal cortex or the hippocampus in rats (9). Entorhinal lesions have shown to stimulate septal cholinergic afferents to proliferate into the dentate molecular layer deprived of perforant path input (21). Thus, glutamatergic and cholinergic systems in the temporal-hippocampal region seem to be the most relevant transmitter systems to be investigated in this study.

The purpose of the present study was to examine pharmacologically potential neurochemical involvement in the compensatory processes taking place in rats with the double lesion. The neurochemical system involved might be particularly vulnerable to the administration of an antagonist. The use of either a cholinergic or glutamatergic antagonist may be expected to cause a reappearance of the recovered deficit in preference for novelty. Because cholinergic as well as glutamatergic antagonists can affect the behavior of intact rats, differential effects on rats with combined lesions and sham-operated control animals will be of particular interest. The antagonists selected were the cholinergic muscarinic receptor blocker atropine sulfate and the glutamatergic NMDA receptor blocker 3-amino-1-hydroxy-2-pyrrolidinone (HA-966). Both atropine sulfate and HA-966 have been demonstrated to interfere with cognitive behavior in rats (24,25).

A modified version of the novelty test of Berlyne (2) consisting of three different sets of stimuli (visual/tactile, olfactory, visual only) has previously been used (16). However, during late testing, it was observed that separate TC/LEC or PP lesions did not cause reduced preference for smell as novelty (Myhrer and Wangen, unpublished data). Thus, the session with olfactory stimulus was not used in the present study.

METHOD

Subjects

Forty-eight male Wistar rats from a commercial supplier (Møllegaard Breeding Laboratories, Denmark), weighing 290–320 g at the time of surgery, served as subjects. The experimental protocol was approved by the Norwegian committee for work with laboratory animals. The rats were randomly assigned to six groups: eight rats were sham operated and received saline, eight were sham operated and received atropine, eight were sham operated and received HA-966, eight received combined TC/LEC + PP lesions and saline, eight received combined lesions and atropine, and eight received combined lesions and HA-966. Their group assignment was not known during testing. The rats were housed individually and had free access to commercial rat pellets and water. They were handled individually 3 days preoperatively and 1 day postoperatively, being allowed to explore a table top (80×60 cm) for 3 min a day. The climatized (21°C) vivarium was illuminated from 0700 to 1900 h.

Surgery

The rats were anesthetized IP with diazepam (10 mg/kg) and fentanyl fluanisone (2 mg/kg) and placed in a stereotaxic head holder with their skulls horizontal. The bilateral TC/LEC lesions were made mechanically by means of the sharp edges of cannulas (dia. 0.5 mm) provided with a collar to control for the insertion depth. The cannula to be used was mounted on a syringe. The point of insertion was 7.8 mm posterior to bregma and 6.7 mm lateral to midline. Each cannula was inserted into the brain in a position deviating 20° from the vertical in the sagittal plane (tip of cannula pointing rostrally). From this position the syringe was moved seven times back and forth in an axis deviating about 45° from the frontal plane (opening of angle pointing medially). These maneuvers were carried out in two stages with insertion depths 6 and 8 mm from top of skull. In this way, the distal part of the angular bundle was transected at a site corresponding approximately to the level of the rhinal fissure.

PP lesions were made in the same way as described for TC/LEC lesions. The point of cannula insertion was 8.5 mm posterior to bregma and 5.0 mm lateral to midline. Each cannula was inserted into the brain in a position deviating 20° from the vertical in the sagittal plane (tip of cannula pointing rostrally). From this position the syringe was moved seven times back and forth in the frontal plane making a cut of 1.0–1.5 mm through the angular bundle. These maneuvers were carried out in three stages with depth of insertions 4, 6, and 8 mm from surface of the skull to tip of cannula. The sham-operated rats received a corresponding incision in the scalp only.

Histology

Upon termination of testing, the animals were decapitated, and the brains were removed and frozen. The brains were sectioned horizontally on a CO_2 freezing microtome at 30 μm, every 12th section being preserved. The sections were stained with methylene blue. The extent of fibers transected was estimated from the degree to which the white matter between TC and LEC was damaged at the three dorsoventral levels presented in Fig. 1. The white matter (not the alveus) was divided in four equal columns, each column representing 25% of the fibers. The occurrence of damage was evaluated under ×75 magnification in a light microscope. The number of columns affected at each dorsoventral level were counted, and the mean percentage of damage was computed for each animal.

The percentage of PP damage was based on the location and extent of the transections in relation to the course of PP fibers. The lesions were traced on diagrams of the PP fibers consisting of 20 lines evenly distributed, each line representing 5% of the fibers. The number of lines affected in the dorsoventral levels presented in Fig. 1 were counted, and the average percentage of damage for each animal was computed.

Administration of Drugs

Atropine sulfate injected IP in a dose of 50 mg/kg 15–20 min before testing has often been used in behavioral studies (25). In the present study, atropine (Sigma Chemical Co., St. Louis, MO) was administered 30 min prior to testing (45 min before presentation of novelty) in a dose of 40 mg/kg, because a dose of 50 mg/kg has previously been shown to profoundly interfere with the behavior of normal rats in the present test (13). (±)-HA-966 (Research Biochemicals Inc., Natick, MA) was injected IP in a dose of 30 mg/kg (1) 1.5 h before start of testing, so that overt signs of sedative effect had disappeared during testing (12). Physiological saline was injected IP in a dose of 0.3 ml.

Apparatus

Behavioral testing was carried out in a Plexiglas cage ($54 \times 33 \times 20$ cm) with a metal mesh roof previously described (11). In brief, the floor was divided in 18 equal squares (9×11 cm). Three identical metal cubes ($5 \times 5 \times 5$ cm) were evenly distributed in the cage in fixed positions (the neutral objects). Two other cubes made up the novel objects. One object only differed from the neutral ones in that its top was uneven with tracks (2 mm) in it making up a square pattern (visual/tactile

stimuli). Because the rats could perceive the tracks or the squares (16 squares measuring 1.1 × 1.1 cm) by bodily contact, both tactile and visual sensory modalities might be used. One was smaller than the neutrals, and two sides were slightly uneven (visual stimulus). All objects were painted light gray. The sound attenuated testing room was provided with a fan producing white noise (52 dB).

Procedure

Adaptation started on postoperative day 14. The rats were allowed to explore individually the empty apparatus for 20 min. On the next day the rats were run in session I. In phase 1, the animals were tested for 5 min in the box with three neutral objects present. The following behaviors were recorded: number of seconds in contact with each object, number of squares traversed (locomotor activity), and number of rearings. Then the rats spent 10 min in the home cage. In phase 2, the rats were tested again for 5 min, and one of the neutral objects had been replaced by the novel object with uneven top. During this period of time the same measures as in phase 1 were made. In session II (postoperative day 16), the same procedure was followed, and the novelty was represented by a smaller object. The testing was carried out in a counterbalanced order; i.e., half of the animals in each group was first tested in session I and the other half was first tested in session II. Only the neutral cube in the middle position was replaced by a novel object. Prior to testing, the apparatus and objects were carefully cleaned and allowed to dry to remove all olfactory cues.

Statistics

Overall analyses were carried out with one-way or two-way ANOVA. Group comparisons were made with Tukey–Kramer multiple comparisons test. Computations were carried out with InStat statistical software program (GraphPad Software, USA) or the SigmaStat (SigmaStat Software, USA).

RESULTS

Histology

The combined lesions appeared similar for all three groups. The TC/LEC lesions were bilateral in all animals. The fiber transections, which often affected the alveus of the hippocampus, were 0.5–1.0 mm long in rostrocaudal extent and 3–4 mm long in dorsoventral extent (Figs. 1 and 2). The mean percentage of fiber lesion was about 95 for all groups. Because about one-third of the fibers are not accessible for denervation, a total of about 60% of the fibers between TC and LEC were disconnected. The perforant path was damaged bilaterally in the entire dorsoventral extent in all rats by a cut of 1.0–1.5 mm in length (Figs. 1 and 2). The mean percentage of fiber damage was about 96 for all groups. Additional lesion was occasionally observed as a relatively small cut in parts of LEC and parasubiculum. The combined lesions were often seen to have fused together and were more extensive than the sum of separate lesions would be expected to make up (16). In the saline-treated group, the mean percentage of fiber damage was 95.3 for the TC-LEC connections (range 91–100) and 96.6 for PP (range 92–100). In four rats, the ventral part of the hippocampal region was damaged unilaterally. In the atropine-treated group, the mean percentage of fiber damage was 95.1 for the TC-LEC connections (range 88–98) and 96.3 for PP (range 91–100). In three rats, the ventral tip of the hippocampal region was damaged unilaterally. In the HA-966–treated group, the mean percentage of fiber damage was 96.7 for the TC-LEC connections (range 91–100) and 96.0 for PP (range 92–100). In four rats the ventral tip of the hippocampal region was damaged unilaterally. In all lesioned groups, the penetrations of neocortical layers with the cannulas left hardly detectable marks. Additional damage other than that reported above could not be observed with the histological method applied.

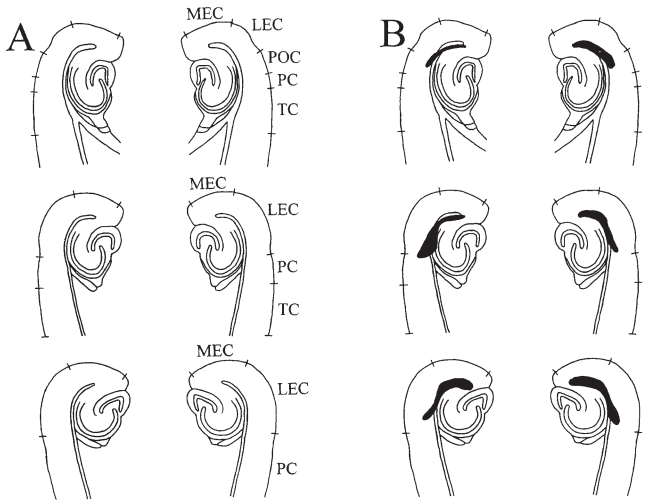

FIG. 1. Reconstruction of horizontal sections indicating normal anatomy (A) and typical example of the combined transections of the temporal-entorhinal connections and the perforant path for all groups (B). Abbreviations: LEC = lateral entorhinal cortex; MEC = medial entorhinal cortex; PC = perirhinal cortex; POC = postrhinal cortex; TC = temporal cortex.

Behavior

Rats treated with atropine or HA-966 displayed reduced preference for novelty compared to saline-treated animals throughout both sessions. However, various degrees of deficiencies were seen among lesioned and sham-operated rats treated with atropine or HA-966 (Table 1). Exploration of neutral object is based on the mean time of contact with the

FIG. 2. Photograph of a horizontal section showing typical appearance of the lesion following combined temporal-entorhinal and perforant path transections.

two neutral ones. Group comparisions were made in terms of difference between exploration of novel vs. neutral objects. An overall analysis with two-way ANOVA showed a significant effect of group, $F(5, 84) = 67.8254$, $p < 0.0001$, but not of sessions, $F(1, 84) = 0.0719$, $p = 0.7892$, or group × session interaction, $F(5, 84) = 0.6583$, $p = 0.6561$. In session I (uneven top of novel object), one- way ANOVA confirmed a significant treatment effect, $F(5, 42) = 33.428$, $p < 0.0001$. Group comparisions with Tukey–Kramer post hoc test showed that the sham + atropine group, sham + HA-966 group, lesion + atropine group, and lesion + HA-966 group exhibited reliably less preference for novelty than the sham + saline and lesion + saline group ($p < 0.001$). However, the lesion + atropine group was even more deficient in this respect than the sham + atropine, sham + HA-966, and lesion + HA groups ($p < 0.001$). Neither the sham + saline and lesion + saline groups nor the sham + atropine, sham + HA-966, and lesion + HA-966 groups differed reliably from one another. In session II (smaller object), ANOVA revealed a significant overall effect, $F(5, 42) = 33.531$, $p < 0.0001$. The sham + atropine, sham + HA-966, lesion + atropine and lesion + HA-966 groups displayed reliably less preference for novelty than the sham + saline and lesion + saline groups ($p < 0.001$). The lesion + atropine rats also showed less preference for novelty than the sham + atropine, sham + HA-966, and lesion + HA-966 rats ($p < 0.01$). No other reliable differences were observed among the animals.

Table 1 shows the total time spent in exploring neutral objects in phase 1 and neutral plus novel objects in phase 2. ANOVAs confirmed significant differences among the groups for both phases in session I and in phase 2 for session II ($p < 0.02$). In all instances, the sham + atropine group explored reliably less than the sham + HA-966 and lesion + saline groups in phase 1 in session I, the sham + saline and lesion + saline groups in phase 2 in session I, and the sham + saline, lesion + saline, and lesion + atropine groups in phase 2 in session II ($p < 0.05$). In phase 2 in session I, the lesion + saline group explored reliably more than the sham + HA-966, lesion + atropine, and lesion + HA-966 groups ($p < 0.05$). The sham + saline group explored significantly more than the lesion + atropine group ($p < 0.05$).

Figure 3A shows that the groups differed in terms of locomotor activity. ANOVAs confirmed reliable differences for all phases in all sessions ($p < 0.002$). In phase 1 in session I, the sham + atropine group was significantly less active than all the other groups ($p < 0.01$). In phase 2, the sham + atropine animals displayed reliably less locomotion than the sham + HA-966, lesion + atropine, and lesion + HA-966 groups ($p < 0.05$). The lesion + atropine group was significantly more active than the lesion + HA-966, lesion + saline, and sham + saline groups ($p < 0.05$). In phase 1 in session II, the sham + atropine rats were reliably less active than the sham + HA-966, lesion + saline, lesion + HA-966, and lesion + atropine animals ($p < 0.05$). In phase 2, the sham + atropine group displayed significantly less activity than the lesion + saline and lesion + atropine groups ($p < 0.05$).

Figure 3B shows that there are differences in rearing activity among the groups. ANOVAs confirmed reliable treatment effects throughout both sessions ($p < 0.002$). In phase 1 in session I, the sham + atropine group made significantly less rearing than all the other groups except the sham + HA-966 and lesion + HA-966 groups ($p < 0.05$). The latter groups made significantly less rearing than the lesion + atropine group ($p < 0.05$). In phase 2, the lesion + atropine rats displayed reliably more rearing than all the other animals ($p < 0.01$). In phase 1 in session II, the lesion + atropine group exhibited significantly more rearing than the sham + saline and sham + atropine groups ($p < 0.05$). In phase 2, the lesion + atropine group made reliably more rearing than the sham + atropine, sham + HA-966, and lesion + HA-966 groups ($p < 0.05$). The sham + atropine animals displayed significantly less rearing than the sham + saline and lesion + saline rats ($p < 0.05$).

DISCUSSION

The present results show that a spontaneous recovery of function had taken place in rats with combined TC/LEC + PP lesions treated with saline, because the behavior of the latter animals did not differ from that of the saline-treated sham-operated rats in any measures. Administration of atropine sulfate resulted in a complete reappearance of the initial effects of the combined lesion (cf. Introduction). The preference for novelty was only moderately reduced in sham-operated rats treated with atropine and in both sham- and lesion-operated rats treated with HA-966. Only atropine caused differential effects in exploratory activity measures between sham and lesion-operated animals.

The marked effect of the cholinergic antagonist relative to the glutamatergic antagonist on lesioned animals suggests that cholinergic systems are more involved in the compensatory processes than glutamatergic ones. In a previous study, it was observed neurochemical changes following separate and combined

TABLE 1
MEAN MEASURES OF EXPLORATORY BEHAVIOR IN SECONDS

		Differential Time Exploring						Total Time Exploring			
		Session I			Session II			Session I		Session II	
Group	*n*	Neut	Nov	Diff	Neut	Nov	Diff	Ph1	Ph2	Ph1	Ph2
Sham + Sal	8	6.1	20.3	14.5	6.3	21.6	15.4	29.9	32.5	21.9	34.1
Sham + Atro	8	2.6	9.9	7.3†	2.4	8.9	6.5†	17.9*	15.1*	13.1	13.6*
Sham + HA	8	5.1	11.4	6.3†	5.1	11.9	6.8†	35.0	21.6	22.1	22.0
Lesion + Sal	8	7.4	22.1	14.8	6.4	21.0	14.6	36.0	36.9	27.5	33.8
Lesion + Atro	8	6.6	5.5	−1.1†	10.1	10.6	0.5†	30.3	18.8	29.6	30.9
Lesion + HA	8	5.3	11.4	6.1†	5.3	11.6	6.4†	32.1	21.9	21.0	22.1

Abbreviations: Atro = atropine; Diff = difference; HA = HA-966; Neut = neutral; Nov = novel; Sal = saline.
*$p < 0.05$.
†$p < 0.001$ significant differences from saline-treated groups.

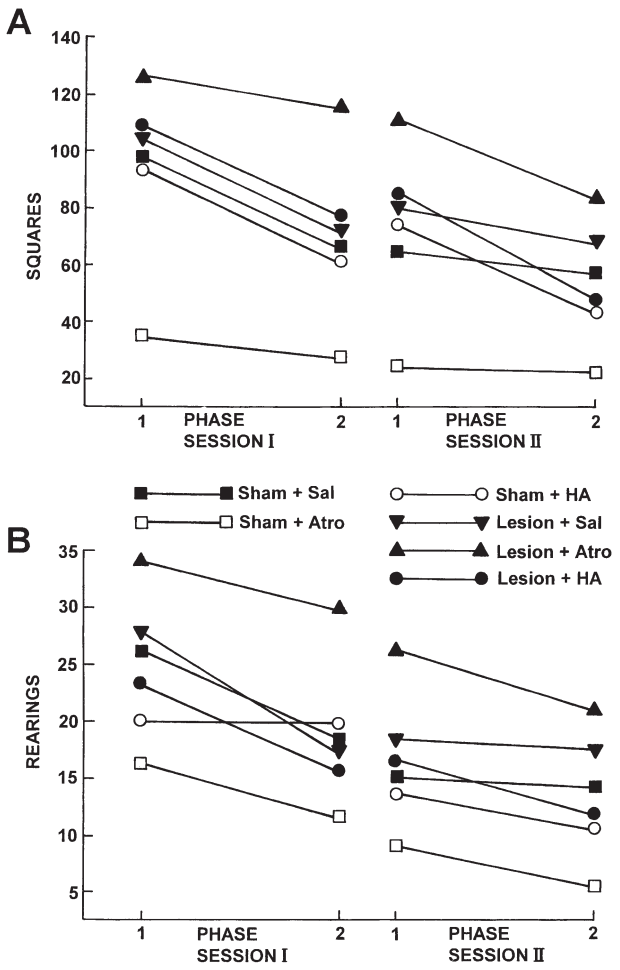

FIG. 3. Mean measures of locomotor activity (A) and rearing (B).

lesions, which suggest a compensatory optimal level of cholinergic activity in the hippocampal region associated with the recovery of function in rats with TC/LEC+PP lesions (16). In the latter study, glutamatergic measures seemed to be unresponsive. Collectively, these findings may imply that restoration of function in animals with the double lesion at least involves an atropine-sensitive mechanism. However, this mechanism cannot be causally related to the hippocampal region. Furthermore, it cannot be ruled out that neurotransmitter systems other than those examined in this study or an upregulation of peptidergic systems may contribute to the functional recovery observed.

Cholinergic systems are well known to respond compensatorily to neural insult. Entorhinal lesions have been reported to produce sprouting in the hippocampal fascia dentata in rats within 9–12 days (18). It has been proposed that this event is due to septo-dentate afferents that can proliferate in response to entorhinal damage (17). Entorhinal lesions functionally similar to TC/LEC + PP lesions cause increased cholinergic activity in the hippocampal region, reaching a peak point at 8 days of survival (21). The combination of TC/LEC + PP lesions appears to counteract the loss of cholinergic terminals seen to follow separate PP transections (16). It may be hypothesized that the combination of lesions damaged a sufficient number of fibers in the white matter to trigger a compensatory activity. Such activity may involve cholinergic projections, because the cholinergic antagonist, atropine sulfate, completely disrupted the functional recovery otherwise seen. A corresponding mechanism is found in aging rats when cholinergic septal grafts into the hippocampal formation improves spatial learning and memory. Administration of atropine completely abolished the recovered learning abilities in the old animals (7).

If acetylcholine is involved in the compensatory process in rats with TC/LEC + PP lesions, it would be of interest in future research to determine the rate of acetylcholine release in different brain regions while these rats recover. Furthermore, it would also be of interest to examine effects of *N*-methylscopolamine vs. scopolamine to determine whether there are any peripheral influences to the recovery.

The differential effects of atropine on lesioned and sham-operated rats suggest that this agent disrupts compensatory cholinergic processes in rats bearing TC/LEC + PP transections, whereas the reduction in preference for novelty seen in normal animals may be related to a general depressing effect on muscarinic receptors. The increased level of locomotor and rearing activities measured in atropine-treated rats with combined lesions is not observed during early testing of rats with such lesions (Myhrer and Wangen, unpublished results). This lack of correspondence may be associated with complex interaction in effects between atropine and the combined lesions, because administration of atropine to intact rats has reverse effect on exploratory behavior (cf. Fig. 3).

The relatively mild disruptive effect of HA-966 on the recovered perference function may be related to inadequate neurotransmission by glutamate in critical areas, because separate TC/LEC and PP lesions impair glutamatergic systems (16,23). Glutamate and glutamate receptors are closely related to learning and memory (6), whereas cholinergic systems seem to be more associated with attentional processes than learning and memory as such (4,19). Thus, atropine and HA-966 may interfere with preference for novelty in different manners. Atropine-treated rats probably pay less attention to environmental change in the present test situation. HA-966 may interfere with encoding of new information resulting in reexamination of objects already inspected. The present novelty test appears to be rather sensitive to effects of atropine, because even a relatively small dose (40 mg/kg) resulted in marked changes in the behavior of normal rats. Effects of 50 mg/kg atropine are not seen in control rats of the same age as those used in the present study in the Morris water maze (7). Intact rats treated with atropine displayed lower levels of total time exploring objects, locomotion, and rearing than saline-treated intact animals. The lesion + atropine group tended to exhibit more locomotor and rearing activity than the sham + saline group. This difference may suggest that the lack of preference for novelty was confounded by a nonspecific effect of the drug on the lesioned rats' motor performance. However, this suggestion appears unlikely in view of the finding that the lesion + atropine rats explored all objects to a similar rate as saline-treated controls. In one instance (phase 2 in session I), the lesion + atropine group explored even less than the sham + saline group.

Atropine and HA-966 were injected at different times prior to testing (cf. administration of drugs) in order to obtain optimal effects of both agents and to avoid the anxiolytic-like effect seen to follow shortly after administration of HA-966 (1). This time difference is not likely to explain the more pronounced effect of atropine on preference for novelty than HA-966 in lesioned animals, because (±)-HA-966 still antagonizes the mitigating effect of glycine in rats with lesioned-induced amnesia more than 2 h after injections. Glycine alone has optimal effect on memory function after the same period of time (12).

REFERENCES

1. Anthony, E. W.; Nevins, M. E.: Anxiolytic-like effects of *N*-methyl-D-aspartate-associated glycine receptor ligands in the rat potentiated startle test. Eur. J. Pharmacol. 250:317–324; 1993.
2. Berlyne, D. E.: Novelty and curiosity as determinants of exploratory behaviour. Br. J. Psychol. 41:68–80; 1950.
3. Berlyne, D. E.: Conflict, arousal, and curiosity. New York: McGraw-Hill; 1960.
4. Blokland, A.: Acetylcholine: A neurotransmitter for learning and memory? Brain Res. Rev. 21:285–300; 1996.
5. Deacon, T. W.; Eichenbaum, H.; Rosenberg, P.; Eckman, K. W.: Afferent connections of the perirhinal cortex in the rat. J. Comp. Neurol. 220:168–190; 1983.
6. Fonnum, F.; Myhrer, T.; Paulsen, R. E.; Wangen, K.; Øksengård, A. R.: Role of glutamate and glutamate receptors in memory function and Alzheimer's disease. Ann. NY Acad. Sci. 757:475–486; 1995.
7. Gage, F. H.; Björklund, A.: Cholinergic septal grafts into the hippocampal formation improve spatial learning and memory in aged rats by an atropine-sensitive mechanism. J. Neurosci. 6:2837–2847; 1986.
8. Insausti, R.; Herrero, T.; Witter, M. P.: Entorhinal cortex of the rat: Cytoarchitectonic subdivisions and the origin and distribution of cortical efferents. Hippocampus 7:146–183; 1997.
9. Jaskiw, G. E.; Tizabi, Y.; Lipska, B. K.; Kolachana, B. S.; Wyatt, R. J.; Gilad, G. M.: Evidence for a frontocortical-septal glutamatergic pathway and compensatory changes in septal glutamate uptake after cortical and fornix lesions in the rat. Brain Res. 550:7–10; 1991.
10. Köhler, C.: Cytochemical architecture of the entorhinal area. In: Schwarcz, R.; Ben-Ari, Y., eds. Exitatory amino acids and epilepsy. New York: Plenum Press; 1986:83–98.
11. Myhrer, T.: The role of medial and lateral hippocampal perforant path lesions and object distinctiveness in rats' reaction to novelty. Physiol. Behav. 42:371–377; 1988.
12. Myhrer, T.: Evidence for activation of NMDA receptors when memory function is reinstated in rats with glutamatergic temporal systems disrupted. Brain Res. 662:263–267; 1994.
13. Myhrer, T.; de Groot, D. M. G.: Immobility-related hippocampal theta activity in rats during reaction to novelty. Scand. J. Psychol. 29:214–222; 1988.
14. Myhrer, T.; Iversen, E. G.; Fonnum, F.: Impaired reference memory and reduced glutamergic activity in rats with temporo-entorhinal connections disrupted. Exp. Brain. Res. 77:499–506; 1989.
15. Myhrer, T.; Paulsen, R. E.: Memory dysfunction following disruption of glutamergic systems in the temporal region of the rat: Effects of agonistic amino acids. Brain Res. 599:345–352; 1992.
16. Myhrer, T.; Wangen, K.: Reduced cognitive dysfunctions in rats when the temporal-entorhinal cortices and hippocampal region are denervated simultaneously. Psychobiology 24:281–293; 1996.
17. Parent, A.; Dea, D.; Quirion, R.; Poirier, J.: [^{3}H] Phorbol ester binding sites and neuronal plasticity in the hippocampus following entorhinal cortex lesions. Brain Res. 607:23–32; 1993.
18. Ramirez, J. J.; Labbe, R.; Stein, D. G.: Recovery from perseverative behavior after entorhinal cortex lesions in rats. Brain Res. 459:153–156; 1988.
19. Robbins, T. W.; Everitt, B. J.; Marston, H. M.; Wilkinson, J.; Jones, G. H.; Page, K. J.: Comparative effects of ibotenic acid- and quisqualic acid-induced lesions of the substantia innominata on attentional function in the rat: Further implications for the role of cholinergic neurons of the nucleus basalis in cognitive processes. Behav. Brain Res. 35:221–240; 1989.
20. Room, P.; Groenewegen, H. J.: Connections of the parahippo campal cortex. I. Cortical afferents. J. Comp. Neurol. 251:415–450; 1986.
21. Storm-Mathisen, J.: Choline acetyltransferase and acetylcholinesterase in fascia dentata following lesion of the entorhinal afferents. Brain Res. 80:181–197; 1974.
22. Swanson, L. W.; Köhler, C.: Anatomical evidence for direct projections from the entorhinal area to the entire cortical mantle in the rat. J. Neurosci. 6:3010–3023; 1986.
23. Taxt, T.; Storm-Mathisen, J.: Uptake of D-aspartate and L-glutamate in excitatory axon terminals in hippocampus: Autoradiographic and biochemical comparison with γ-aminobutyrate and other amino acids in normal rats and rats with lesions. Neuroscience 11:79–100; 1984.
24. Wangen, K.; Myhrer, T.; Moldstad, J. N.; Iversen, E. G.; Fonnum, F.: Modulatory treatment of NMDA receptors in neonatal rats affects cognitive behavior in adult age. Dev. Brain Res. 99:126–130; 1997.
25. Whishaw, I. Q.; Petrie, B. F.: Cholinergic blockade in the rat impairs strategy selection but not learning and retention of non-spatial visual discrimination problems in a swimming pool. Behav. Neurosci. 102:662–677; 1988.